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**(54) Title:** ALBUTEROL SULFATE SUSPENSION AEROSOL FORMULATIONS

**(57) Abstract**

Suspension aerosol formulations comprising albuterol sulfate, oleic acid, ethanol and 1,1,1,2-tetrafluoroethane.

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# ALBUTEROL SULFATE SUSPENSION AEROSOL FORMULATIONS

## FIELD OF THE INVENTION

This invention relates to suspension aerosol formulations suitable for the administration of medicaments. In another aspect, it relates to pharmaceutical suspension aerosol formulations containing albuterol sulfate and in yet another aspect to aerosol formulations using 1,1,1,2-tetrafluoroethane as the propellant.

## BACKGROUND OF THE INVENTION

Albuterol sulfate is a relatively selective beta$_2$-adrenergic bronchodilator. It is available in a variety of different dosage forms including tablets, syrups and formulations suitable for inhalation. For example, VENTOLIN™ Inhalation Aerosol (commercially available from Allen & Hansburys, Division of Glaxo Inc.; Research Triangle Park, NC) is a metered-dose aerosol unit containing a microcrystalline suspension of albuterol (free base) in propellant (a mixture of trichloromonofluoromethane and dichlorodifluoromethane) with oleic acid. VENTOLIN ROTOCAPS™ for Inhalation (commercially available from Allen & Hansburys) contain a mixture of microfine albuterol sulfate with lactose and are intended for use with a specially designed device for inhaling powder. VENTOLIN™ Solution for Inhalation (commercially available from Allen & Hansburys) is an aqueous solution of albuterol sulfate intended for use with a nebulizer.

Chlorofluorocarbons, including dichloromonofluoromethane and dichlorodifluoromethane, have been implicated in the destruction of the ozone layer and their production is being phased out.

Hydrofluorocarbon 134a (1,1,1,2-tetrafluoroethane) is viewed as being less destructive to ozone than many chlorofluorocarbon propellants; furthermore, it has a

low toxicity and a vapor pressure that is suitable for use in aerosols.

SUMMARY OF THE INVENTION

This invention provides suspension aerosol formulations comprising about 0.05 to about 1.5 percent by weight micronized albuterol sulfate, about 0.25 to about 2 percent by weight of oleic acid, about 5 to about 20 percent by weight ethanol, and 1,1,1,2-tetrafluoroethane. This invention also provides a method for inducing bronchodilation in a mammal.

The suspension aerosol formulations of the invention are suitable for oral inhalation.

DETAILED DESCRIPTION OF THE INVENTION

The term suspension aerosol means that the albuterol sulfate is in powder form and is substantially insoluble in the propellant/ethanol blend.

The term micronized means that the albuterol sulfate is in the form of a fine powder, that is, over 90 percent of the particles will have a diameter of less than about 10 microns.

All weight percentages recited herein are based on the total weight of the formulation unless otherwise indicated.

Micronized albuterol sulfate constitutes from about 0.05 to 1.5 percent by weight, preferably from about 0.05 to about 1.3 percent by weight, more preferably about 0.4 to about 0.8 percent by weight, and most preferably about 0.4 to about 0.5 percent by weight of the aerosol formulation.

Oleic acid constitutes from about 0.25 to about 2 percent by weight, preferably from about 0.25 to about 1.0 percent by weight, more preferably about 0.25 to

about 0.75 percent by weight, and most preferably about 0.5 percent by weight of the aerosol formulation.

Ethanol constitutes from about 5 to about 20 percent by weight, preferably about 12 to about 17 percent by weight, and most preferably about 15 percent by weight of the aerosol formulation.

Preferably, the aerosol formulations of this invention do not contain a propellant other than 1,1,1,2-tetrafluoroethane. Most preferably, the aerosol formulations of the present invention do not contain ingredients other than 1,1,1,2-tetrafluoroethane, ethanol, oleic acid, and albuterol sulfate.

A particularly preferred formulation according to the invention comprises, in addition to 1,1,1,2-tetrafluoroethane, about 0.40 to about 0.42 percent by weight of albuterol sulfate, about 0.5 percent by weight of oleic acid, and about 15 percent by weight ethanol.

The suspension aerosol formulations of this invention can be prepared by first preparing a solution of oleic acid and ethanol in 1,1,1,2-tetrafluoroethane and then suspending the albuterol sulfate in the solution. In order to prepare a formulation in this manner, the oleic acid and ethanol are placed in an aerosol vial, then 1,1,1,2-tetrafluoroethane is added. The vial is then sealed with a continuous valve. The micronized albuterol sulfate is placed in a separate aerosol vial, a continuous valve is crimped onto the vial and the vial is pressure filled with the previously prepared solution. The albuterol sulfate is then dispersed in the solution by mixing or homogenizing. Alternatively, the formulations can be prepared by first placing the micronized albuterol sulfate, the oleic acid and ethanol in an aerosol vial. In order to prepare a formulation in this manner, a continuous valve is crimped onto a vial containing the

micronized albuterol sulfate, the oleic acid, and the ethanol. The vial is then pressure filled with 1,1,1,2-tetrafluoroethane and shaken to disperse the albuterol sulfate.

Preferred formulations of this invention exhibit substantially no growth in particle size or change in crystal morphology of albuterol sulfate over a prolonged period, are substantially and readily redispersible, and upon redispersion do not flocculate so quickly as to prevent reproducible dosing of albuterol sulfate.

The following examples are provided to illustrate the invention but should not be construed as limiting the invention. Particle size, respirable fraction, and medication delivery are determined using the test methods described below.

Particle Size Assay

In this assay, metered dose(s) of the aerosol formulation are actuated into filtered Propellant 113 using a needle fitted for an aerosol valve. The particle size distribution of the resulting suspension is then analyzed using a laser diffraction particle size analyzer.

The particle sizer used is a Malvern 2600c Particle Sizer (available from Malvern; Worcestershire, UK) equipped with a 63mm lens, a PS1 Stirred Liquid Cell and MasterSizer Software Version 5.4. The suspending liquid is filtered Propellant 113.

The aerosol vial to be tested is shaken and primed five times into a vented area away from the analyzer and the suspending liquid. The inside of the valve stem, the needle, and the adapter are then flushed with methanol or isopropanol followed by a flush with filtered Propellant 113. All parts are then thoroughly dried with pressurized air. The aerosol vial is fitted into the needle, the end of the needle

is submerged into the sample cell, and the aerosol vial is actuated. Actuation is repeated (if necessary) until the obscuration value is in the range of 0.15 to 0.30. The sample is then analyzed and the percent of particles under 3.0 microns, 5.0 microns and 10.5 microns is reported for each sample.

Respirable Fraction

In this assay the respirable fraction (the percent of particles having an aerodynamic particle size of less than 4.7 microns) of the aerosol suspension is determined using an Anderson Cascade Impactor (available from Anderson Sampler Inc.; Atlanta, GA).

The aerosol vial to be tested is primed five times. The valve and valve stem are then cleaned with methanol and dried with compressed air. The aerosol vial and a clean, dry actuator are coupled to the glass throat attached to the top of the impactor using an appropriate firing adapter. The calibrated vacuum pump (28.3 L/min) attached to the cascade impactor is turned on. A total of 20 sprays is delivered into the cascade impactor by repeatedly shaking the vial, seating it in the actuator and then immediately delivering a single spray. The time between sprays is approximately 30 seconds. The cascade impactor is disassembled and each component is rinsed separately with diluent (45 parts of methanol mixed with 55 parts 0.1% phosphoric acid, v/v). Each solution is analyzed for albuterol sulfate content using high pressure liquid chromatography. The respirable fraction is calculated as follows:

$$\% \text{ respirable} = \frac{\text{drug recovered from plates 3-7}}{\text{total drug recovered} - \text{drug recovered from actuator and valve}} \times 100$$

Medication Delivery Assay

This assay measures the amount of albuterol sulfate delivered per shot.

Approximately 20 mL of sample diluent (prepared by mixing 45 parts of methanol with 55 parts of 0.1% phosphoric acid, v/v) is placed into the gas washing bottle of the Artificial Respiratory System (USP XXI). The aerosol vial and actuator are coupled to the intake tube of the Artificial Respiratory System (ARS) using an appropriate firing adapter. A total of 4 sprays is delivered into the ARS by repeatedly shaking the vial, seating it in the actuator, applying vacuum (12 ± 1 liter per minute) and immediately delivering a single spray. The vial is separated from the actuator after each spray. After all 4 sprays are delivered, the aerosol vial, actuator and firing adapter are uncoupled from the intake tube. The gas washing bottle, firing adapter and intake tube are rinsed with diluent. The rinses are combined with the diluent originally placed in the gas wash bottle and analyzed for albuterol sulfate content using high pressure liquid chromatography.

Example 1

A 0.25 g portion of oleic acid was placed in a 4 ounce vial, 5.0 g of ethanol was added and then 94.25 g of cold (about -65°C) 1,1,1,2-tetrafluoroethane was added. A continuous valve was sealed onto the vial immediately after the addition of the 1,1,1,2-tetrafluoroethane. The resulting stock solution contained 0.25% by weight of oleic acid and 5.0 % by weight of ethanol. A 100 mg portion of micronized albuterol sulfate was placed in each of four 15 mL glass aerosol vials along with 5 mL of glass beads. The vials were sealed with continuous valves and then charged with approximately 20 g of the stock solution. The vials were shaken on a WIG-L-BUG™ mixer

for at least 30 seconds. The resulting aerosol suspension formulations contained 0.5% by weight of albuterol sulfate. The vials were chilled in dry ice, the valves were removed and the vial contents were transferred to four 15 mL aluminum vials. The vials were sealed with 25 microliter Spraymiser™ (available from Neotechnic; Clithroe, UK) valves. Using the test method described above, the respirable fraction was determined in duplicate. Values of 52.7% and 51.6% were obtained.

Example 2

Using the method of Example 1, aerosol suspension formulations containing 0.5% by weight of oleic acid, 15.0% by weight of ethanol and 0.5% by weight of albuterol sulfate were prepared. The respirable fraction was determined in duplicate. Values of 26.3% and 23.1% were obtained.

Examples 3-5

Using the method described below, a series of suspension aerosol formulations containing 0.5% by weight of micronized albuterol sulfate were prepared. Table 1 shows the amount (percent by weight based on the total weight of the formulation) of oleic acid and ethanol used. A 0.1 g portion of micronized albuterol sulfate was added to each of three 15 mL glass aerosol vials containing 5 mL portions of glass beads. Oleic acid and ethanol were added to the vials which were then immediately sealed with continuous valves. 1,1,1,2-tetrafluoroethane was added through the valve by using a pressure buret. The vials were then shaken on a WIG-L-BUG™ mixer for at least 30 seconds. The resulting suspensions were transferred to 15 mL aluminum aerosol vials and sealed with 25 microliter Spraymiser™ valves. The respirable fractions were

determined in duplicate using the test method described above. The values obtained are shown in Table 1.

TABLE 1

| Example | Oleic Acid | EtOH | Respirable Fraction | |
|---|---|---|---|---|
| 3 | 0.5% | 15% | 23.0% | 34.3% |
| 4 | 1.0% | 10% | 26.6% | 26.4% |
| 5 | 1.0% | 20% | 15.3% | 17.6% |

Examples 6-10

Using the general method of Examples 3-5, a series of suspension aerosol formulations containing 1.0% by weight of oleic acid and 0.5% by weight of micronized albuterol sulfate were prepared. Table 2 shows the amount (percent by weight based on the total weight of the formulation) of ethanol contained in each formulation. After the formulations had been maintained at room temperature for 42 days, the particle size of the albuterol sulfate was determined using the assay described above. The vials were then placed in a cycling (the temperature is cycled from 4°C to 40°C every 6 hours) chamber. Particle size analysis was performed after 15 days and 22 days. The results of the particle size assays are shown in Table 2. The percent of particles under 3.0 microns, 5.0 microns and 10.5 microns is shown.

TABLE 2

| Example | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|
| EtOH | 10.0 | 12.5 | 15.0 | 17.5 | 20.0 |
| 42 days RT | | | | | |
| 3.0 | 75.8 | 57.6 | 52.5 | 52.8 | 67.1 |
| 5.0 | 95.0 | 86.8 | 80.8 | 80.0 | 92.1 |
| 10.5 | 99.9 | 99.6 | 99.1 | 99.3 | 100.0 |
| 15 days recycling | | | | | |
| 3.0 | 72.2 | 66.3 | 53.7 | 52.8 | 66.4 |
| 5.0 | 95.1 | 92.5 | 93.7 | 92.8 | 91.3 |
| 10.5 | 100.0 | 99.9 | 99.9 | 99.9 | 97.5 |
| 22 days recycling | | | | | |
| 3.0 | 69.0 | 58.5 | 56.5 | 52.0 | 64.1 |
| 5.0 | 94.0 | 87.2 | 93.2 | 90.0 | 92.2 |
| 10.5 | 100.0 | 99.9 | 100.0 | 100.0 | 100.0 |

Examples 11-13

Using the general method of Examples 3-5, a series of suspension aerosol formulations containing 0.5% by weight of oleic acid and 15.0% by weight of ethanol were prepared. Table 3 shows the amount (percent by weight based on the total weight of the formulation) of albuterol sulfate contained in each formulation. The respirable fractions were determined in duplicate using the test method described above. The values obtained are shown in Table 3.

TABLE 3

| Example | Albuterol Sulfate | Respirable Fraction | |
|---|---|---|---|
| 11 | 0.8% | 20.7% | 23.3% |
| 12 | 1.0% | 20.8% | 19.5% |
| 13 | 1.2% | 20.2% | 19.0% |
| 14 | 1.4% | 17.6% | 19.7% |

Examples 15-20

Using the general method of Examples 3-5, a series of suspension aerosol formulations containing 0.5% by weight of oleic acid were prepared. Table 4 shows the amount (percent by weight based on the total weight of the formulation) of ethanol and micronized albuterol sulfate contained in each formulation. These formulations were tested for their ability to deliver a consistent dose throughout the "life" of the aerosol by determining the amount of albuterol sulfate delivered per shot for shots 1-4, 96-100, 196-200, 296-300 and 396-400. The amount delivered per shot was determined using the assay described below. The results are shown in Table 4.

Each aerosol vial being analyzed was primed 5 times into the hood. The valve stem was cleaned with methanol and dried with nitrogen. The vial was then weighed.

A firing disk was placed in a 100 mL beaker and submerged in about 30 mL of diluent (55 parts 0.1% phosphoric acid/45 parts methanol). The vial was shaken, inserted into the firing disk, and actuated. This step was repeated until a total of 4 actuations had been made. The valve and valve stem were rinsed into the beaker with additional diluent. The solution in the beaker was quantitatively transferred to a 100 mL volumetric flask which was then brought to volume with additional diluent. The vial was then dried and

weighed. The amount of albuterol sulfate in the solution was then determined using high performance liquid chromatography.

In order to reach the midpoint of the vial life, the appropriate number of shots were fired (similar to priming). As before, the valve stem was cleaned and dried, and the vial was weighed. The assay was then repeated.

TABLE 4

| Example | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|
| EtOH | 15.0% | 15.0% | 15.0% | 10.0% | 10.0% | 10.0% |
| Albuterol sulfate | 1.5% | 1.25% | 1.0% | 1.5% | 1.25% | 1.0% |
| | micrograms of albuterol sulfate per shot | | | | | |
| Shots 1-4 | 491 | 412 | 337 | 470 | 439 | 344 |
| Shots 96-100 | 448 | 382 | 338 | 471 | 466 | 295 |
| Shots 196-200 | 471 | 395 | 349 | 476 | 402 | 333 |
| Shots 296-300 | 436 | 411 | 323 | 454 | 409 | 336 |
| 396 - 400 | 473 | 391 | 395 | 467 | 443 | 339 |

Example 21

A 8.0 g portion of albuterol sulfate and a 10.0 g portion of oleic acid were placed in a 150 mL beaker. A portion of ethanol was added and the mixture was stirred for at least 3 minutes. The resulting slurry was passed through a pump homogenizing system then collected in a tared beaker. Enough ethanol was added to the beaker to bring the total weight of the concentrate (albuterol sulfate, oleic acid, ethanol) to 318 g. The concentrate was chilled then placed along with 1682 g of chilled 1,1,1,2-tetrafluoroethane into a cold filling system which had been prechilled to about -40°C. Aerosol vials were filled with 14.0 ± 0.5

g of formulation then sealed with 25 μL Spraymiser™ valves. The resulting formulation contained 0.4% by weight albuterol sulfate. The Medication Delivery Assay, described above was performed on two vials. Values of 98.9 μg albuterol sulfate per shot and 98.7 μg albuterol sulfate per shot were obtained. Using the assay described above, the respirable fraction was determined using 8 different vials. Values of 54.9%, 53.7%, 55.7%, 58.0%, 52.8%, 51.9%, 56.0%, and 56.0% were obtained.

WHAT IS CLAIMED IS:

1. A suspension aerosol formulation comprising between about 0.05 and about 1.5 percent by weight micronized albuterol sulfate, between about 0.25 and about 2.0 percent by weight oleic acid, between about 5 and about 20 percent by weight ethanol, and 1,1,1,2-tetrafluoroethane.

2. A suspension aerosol formulation according to Claim 1 wherein said micronized albuterol sulfate is present in an amount of about 0.05 to about 1.3 percent by weight.

3. A suspension aerosol formulation according to Claim 1 wherein said oleic acid is present in an amount of about 0.25 to about 1.0 percent by weight.

4. A suspension aerosol formulation according to Claim 1 wherein said ethanol is present in an amount of about 12 to about 17 percent by weight.

5. A suspension aerosol formulation according to Claim 1 comprising about 0.3 to about 0.6 percent by weight micronized albuterol sulfate, about 0.25 to about 0.75 percent by weight oleic acid, about 15 percent by weight ethanol, and 1,1,1,2-tetrafluoroethane.

6. A suspension aerosol formulation according to Claim 1 consisting essentially of between about 0.05 and about 1.5 percent by weight micronized albuterol sulfate, between about 0.25 and about 2.0 percent by weight oleic acid, between about 5 and about 20 percent by weight ethanol, and 1,1,1,2-tetrafluoroethane.

7. A suspension aerosol formulation according to Claim 1 consisting essentially of about 0.40 to about 0.42 percent by weight albuterol sulfate, about 0.5 percent by weight oleic acid, about 15 percent by weight ethanol, and 1,1,1,2-tetrafluoroethane.

8. A method for causing bronchodilation in a mammal comprising administering to the lungs of said mammal an amount of an aerosol formulation according to Claim 1 effective to result in bronchodilation.

# INTERNATIONAL SEARCH REPORT

International Applicati· o PCT/US 92/04587

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/72 A 61 K 31/135

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

| Classification System | Classification Symbols |
|---|---|
| Int.Cl.5 | A 61 K |

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

| Category ° | Citation of Document, [11] with indication, where appropriate, of the relevant passages [12] | Relevant to Claim No.[13] |
|---|---|---|
| X | EP,A,0372777 (RIKER LABORATORIES, INC.) 13 June 1990, see the whole document, in particular page 6, example 5; page 8, example 20; pages 8,9, examples 24-6 | 1-8 |

° Special categories of cited documents : [10]

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IV. CERTIFICATION

| Date of the Actual Completion of the International Search | Date of Mailing of this International Search Report |
|---|---|
| 12-08-1992 | 09. 04. 92 |
| International Searching Authority: EUROPEAN PATENT OFFICE | Signature of Authorized Officer: Mme Dagmar FRANK |

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# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9204587 SA 61177

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 27/08/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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